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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/788,074	02/16/01	HOTAMISLIGIL	G 21509-044

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EXAMINER	
NGUYEN, L	
ART UNIT	PAPER NUMBER
1635	7

DATE MAILED: 10/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/788,074	HOTAMISLIGIL, GOKHAN S.	
	Examiner	Art Unit	
	Lauren Nguyen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-11, drawn to a method of reducing the level of circulating free fatty acids in a mammal comprising administration of a compound that inhibits expression of Mal1, classified in class 514, subclass 44, for example.

II. Claims 12-15, drawn to a method of reducing the level of circulating free fatty acids in a mammalin comprising administration of a compound that inhibits Mal1 activity, classified in class 514, subclass 44, for example.

III. Claims 16 and 17, drawn to a method of diagnosing insulin resistance or diabetes comprising determining the level of Mal1 transcripts or polypeptide in a tissue sample, classified in class 435, subclass 6, for example.

IV. Claim 18, drawn to a method of diagnosing dyslipidemia or predisposition thereto comprising determining the level of Mal1 transcripts or polypeptide in a tissue sample, classified in class 435, subclass 6, for example.

V. Claim 19, drawn to a method of diagnosing atherosclerosis or predisposition thereto comprising determining the level of Mal1 transcripts or polypeptide in a tissue sample, classified in class 435, subclass 6, for example.

VI. Claim 20, drawn to a method of diagnosing a predisposition to developing obesity comprising determining the level of Mal1 transcripts or polypeptide in a tissue sample, classified in class 435, subclass 6, for example.

These inventions are distinct, each from the other, for the following reasons:

Group I, drawn to a method of reducing the level of circulating free fatty acids in a mammal comprising administration of a compound that inhibits expression of Mal1, is a materially different process comprising of materially different steps with materially different products from that of Group II, a method of reducing the level of circulating free fatty acids in a mammalin comprising administration of a compound that inhibits Mal1 activity. The method of Group I employs nucleic acid products, such as antisense oligonucleotides, for instance, which are materially different from the protein products employed in the method of Group II, such as antibodies for example. Nucleic acids are different chemical entities from proteins and have different chemical and biological properties. Therefore, the examination of Group I would require an additional field of search from the examination of Group II, thereby creating an undue burden upon the Examiner.

Groups I and II are materially different processes from each of Groups III-VI because the methods claimed in Groups III-VI are drawn to method of diagnosing a disease or a predisposition thereto. Groups I and II involve materially different steps with materially different products from that of Groups III-VI because the diagnosis or predisposition of insulin resistance, diabetes, dyslipidemia, artherosclerosis, and obesity require the consideration of additional factors such as regulated levels of Mal1, the correlation of Mal 1 levels of transcript or polypeptide corresponding to the disease state, and the correlation of Mal 1 levels of transcript or polypeptide corresponding to the predisposition of such diseases, for instance. Therefore, the examination of Group I would require an additional field of search from the examination of Group III-VI, thereby creating an undue burden upon the Examiner.

Groups III-VI are distinct, each from the other, because each group is drawn to the diagnosis or predisposition to a different and distinct disease state. First, insulin resistance and diabetes, dyslipidemia, artherosclerosis, or obesity are recognized as divergent subject matters because the pathology differs for each of these diseases. Second, the correlation of Mal 1 levels of transcript or polypeptide corresponding to each of these disease states will differ. Third, the correlation of Mal 1 levels of transcript or polypeptide corresponding to a predisposition of these disease states will also differ. Therefore, a new field of search would be required for examination of each of Groups III-VI, thereby creating an undue burden upon the Examiner.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and because an additional field of search would be required for examination, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ingrid Beattie on August 23, 2001 a provisional election was made without traverse to prosecute the invention of Group III, claims 16 and 17. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-15 and 18-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 16 and 17 are drawn to a method of diagnosing insulin resistance or diabetes or a predisposition thereto in a mammal, comprising determining the level of Mal1 transcripts or polypeptides in a tissue sample, wherein an increase in the level of said transcripts or said polypeptide in said tissue compared to a normal control tissue indicates that said mammal is suffering from or predisposed to developing diabetes or insulin resistance.

The instant specification provides data showing that Mal1 -/- mutant mice have decreased bodymass (Fig. 2) and reduced plasma levels of glucose and insulin (Fig. 3). The instant specification does not provide *in vitro* or *in vivo* data showing that increased levels of Mal1 transcript or polypeptide causes reduced plasma levels of glucose and insulin. Furthermore, the instant specification does not provide *in vitro* or *in vivo* data showing that increased levels of Mal1 transcript or polypeptide renders a predisposition in a mammal to manifest insulin resistance or diabetes. The instant specification does not provide biochemical data demonstrating that there is an established cause-and-effect relationship between increased expression of Mal1 and manifestation or predisposition to insulin resistance or diabetes.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (See *United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed.

Cir. 1988)). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. The Courts, in *Ex parte Forman,* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and later *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) described the standard of undue experimentation as a standard of reasonableness and set forth the various factors to be considered in the determination of enablement for an invention. These factors include the following:

1) *State of the prior art.* The art of diabetes pathology and the involvement of impaired insulin secretion in the manifestation of the diabetes disease state is well understood at the time of filing. However, the art of determining a subject's predisposition to manifesting insulin resistance or diabetes has not been demonstrated in the prior art. Although diabetic subjects display impairments in glucose tolerance and insulin secretion, the prior art has not established that these abnormalities are the primary cause for the manifestation of diabetes. As stated by Pratley *et al.* (Diabetologia, Vol. 44, p. 929-945, 2001), "although cross-sectional studies clearly indicate that persons with diabetes and impaired glucose tolerance manifest impairments in insulin secretion and insulin action, it is not possible to ascertain from these studies whether the observed abnormalities are primary, contributing to the development of the disease, or whether they are secondary to the metabolic derangements such as mild hyperglycemia, inherent in these conditions (p. 936, paragraph 3-p. 937)." Since causative factor leading to the diabetic disease state has not yet been determined, predisposition to diabetes cannot also be determined because the determination of a subject's predisposition to diabetes relies on the evaluation of a causative factor attributing to such a disease, which is, as of the time of filing, not established in the prior art.

The art of diabetes pathology and its association to Mal1 expression has not been reported in the prior art at the time of filing.

2) *Unpredictability of the art.* The art of diabetes pathology and the involvement of impaired insulin secretion in the manifestation of the diabetes disease state was well understood at the time of filing and could be considered as predictable. However, barring family history and diabetic gestational considerations, the art of determining a subject's predisposition to manifesting insulin resistance or diabetes is highly unpredictable at the time of filing. Furthermore, the role of Mal1 expression in the manifestation of the diabetes or insulin resistance disease state and predisposition thereto is highly unpredictable at the time of filing.

3) *Breadth of the claims.* The claims are broadly drawn to method of diagnosing insulin resistance or diabetes or predispositions thereto by determining levels of Mal1 transcripts or polypeptide is a tissue sample, wherein an increase in Mal1 levels indicate insulin resistance or diabetes disease state or predispositions thereto.

4) *Number of working examples.* The instant specification provides data showing that Mal1 -/- mutant mice have decreased bodymass (Fig. 2) and reduced plasma levels of glucose and insulin (Fig. 3).

5) *Amount of guidance presented by applicants.* The instant specification provides data showing that Mal1 -/- mutant mice have decreased bodymass (Fig. 2) and reduced plasma levels of glucose and insulin (Fig. 3). The instant specification does not provide *in vitro* or *in vivo* data showing that increased levels of Mal1 transcript or polypeptide cause reduced plasma levels of glucose and insulin. Moreover, the instant specification does not provide *in vitro* or *in vivo* data showing that increased levels of Mal1 transcript or polypeptide render a predisposition

in a mammal to manifest insulin resistance or diabetes. The instant specification does not provide biochemical data demonstrating that there is an established cause-and-effect relationship or a correlation between increased expression of Mal1 and manifestation or predisposition to insulin resistance or diabetes. In addition, since both claims 16 and 17 are drawn to methods that recite the same steps, it is unclear in view of the lack of guidance within the specification how the ordinary skilled artisan practicing such a method would be able to distinguish insulin resistance from diabetes without specific guidance in the specification about the levels of Mal1 transcripts or polypeptide which would correlate with either disease state, for example. Furthermore, the specification does not provide data for the parallel experiment, demonstration that mice exhibiting the diabetes or insulin resistance disease state have aberrantly higher expression of Mal1 transcripts or polypeptides when compared to healthy mice.

6) *Level of skill in the art.* The level of skill in the diagnosis art of insulin resistance or diabetes or predispositions thereto is high; however, those of preeminent skill in the art (i.e. Pratley *et al.*, cited above) have been unable to reduce to practice methods of diagnosing predispositions to insulin resistance or diabetes, except in cases of family history or gestational diabetes.

7) *Nature of the invention.* The invention involves one of the most complex, unpredictable areas of biochemistry and medicine, the diagnosis of predispositions to insulin resistance or diabetes determined by increased expression of Mal1 transcripts or polypeptides.

Given the above analysis of the factors which the Courts have determined are essential for determining whether a specification provides enablement for a claimed invention, it must be considered that the skilled artisan would have had to have practiced trial and error

experimentation, with little or no guidance from the prior art, in order to try to practice the claimed invention. Such experimentation is the antithesis of enablement under 35 USC 112, first paragraph, and said experimentation must be considered to be undue and excessive. Therefore, one of ordinary skill in the art would have had to perform undue trial and error experimentation in order to make and use the invention of the above claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 16 is objected to because of the following informalities: claim 16 recites "...wherein an increase in the level said transcripts..."; it appears that a preposition such as "of" is missing after recitation of "...level..." in the claim. Appropriate correction is required.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Nguyen, Ph.D. whose telephone number is 703-308-0256. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lauren Nguyen, Ph.D.
October 22, 2001

SEAN McGARRY
PRIMARY EXAMINER